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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,387	10/01/2003	Yoshihide Iwaki	2870-0266P	4434

2292 7590 02/15/2006

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 02/15/2006.

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,387	IWAKI ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *12-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending.

In the Response to Restriction filled 12/23/2005 applicant has elected with traverse the invention of Group I (claims 1-11) drawn to methods for detecting SNPs utilizing particularly designed primers.

Claims 12-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-11) in the reply filed on 12/23/2005 is acknowledged. The traversal is on the ground(s) that a search of the invention of Group I would be coextensive with a search of Group III. This is not found persuasive because the inventions of Groups I and III utilize different modes of operation which are not so closely related as to make a search of the invention of Group I (primer design strategies) coextensive with a search of the invention of Group III (methods utilizing differing numbers of PCR cycles). This is evidenced by the art cited in this office action, as well as the IDS of the instant application, which details various aspects of strategies for the design of allele specific primers that utilize internal artificial mismatches, but that same art is silent on alterations in PCR conditions which affect product yield in an allele-specific manner.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-7, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Newton et al (1997) US Patent 5,595,890.

Regarding claim 1, Newton et al teaches methods for the detection of variant nucleotide sequences using two types of allele specific primers (one primer of a particular sequence corresponding to each particular allele); the reference indicates that by particularly selecting the sequence of the allele specific primer it is possible to selectively achieve primer extension of either a variant or normal sequence (Fig. 1; col.2 ln.66 – col.3 ln.6). Because the selected primers specifically amplify the selected target allele, the amount of amplified product resulting from each primer will be based on the amount of the primer used, and thus will be substantially the same if the amounts of primer in the initial PCR are the same, as in the examples provided in the reference (col.30 ln.25).

Regarding claim 2, Newton et al teaches that the polymorphic position of the analyzed nucleic acid sequence corresponds to the terminal nucleotide of the diagnostic primer (col. 3 ln.18), and specifically provides examples of primer pairs in which the polymorphic position corresponds to the 3' terminal nucleotide of the primers (col.24 lns.24-32), which is within 4 nucleotides of the 3' terminus of the primer.

Regarding claim 3, Newton et al teaches the use of diagnostic primers that contain artificial mismatches (i.e.: mismatches that are in addition to those mismatches present when an allele-specific primer hybridizes to its non-cognate allele target sequence) to increase the specificity of allele specific primers (col.11 lns.52-55; col.12 lns.27-46; col.29 lns.17-35). The reference teaches that an additional mismatch may be positioned 1 base from the terminal mismatch (col.12 ln.31), which would be adjacent to the 3' terminal polymorphism site.

Regarding claim 4, Newton et al teaches that different mismatches in allele specific primers have different hybridization characteristics and thus creates different levels of specificity (col.12 lns.9-22). The reference also teaches that the best design of any particular primer can be determined by experimentation based on such criteria. Such design would include the selection of particular artificial mismatched nucleotides that provide the best specificity for any give allele specific primer.

Regarding claims 5-7, Newton et al teaches the analysis of SNP sites using polymerase reactions such as PCR (col.30 lns.32-47), and the analysis of the products of the reaction by electrophoresis (col.14 lns.27-32; col.30 lns.48-55).

Regarding claim 11, Newton et al teaches allele specific primers can be used for analysis of homo/heterozygosity (col.12 lns.38-42; col.13 lns.35-41; col.21 lns.42-56; Fig.1).

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (1997) US Patent 5,595,890 in view of Durward et al (1998).

Regarding claim 1, upon which claims 8 and 9 are dependent, Newton et al teaches methods for the detection of variant nucleotide sequences using two types of allele specific primers (one primer of a particular sequence corresponding to each particular allele); the reference indicates that by particularly selecting the sequence of the allele specific primer it is possible to selectively achieve primer extension of either a variant or normal sequence (Fig. 1; col.2 ln.66 – col.3 ln.6). Because the selected primers specifically amplify the selected target allele, the amount of amplified product resulting from each primer will be based on the amount of the primer used, and thus will be substantially the same if the amounts of primer in the initial PCR are the same, as in the examples provided in the reference (col.30 ln.25). Newton et al further teaches methods for using allele specific primers to analyze nucleotide variants (col.13 lns.3-41), specifically mentioning point mutations of a corresponding normal sequence (col.15 lns.21-23) (which would include a SNP), and detection via analysis of PCR products.

Newton et al does not teach the analysis of the PCR by-product pyrophosphoric acid (PPi) for the detection step in the analysis of variant nucleotides.

Durward et al teaches a colorimetric method for detecting amplified nucleic acids based on measuring PPi (p.608, right col., lns.23-28). The reference teaches that during the PCR reaction the incorporation of dNMPs from dNTPs into amplified nucleic

acids generates inorganic pyrophosphate (PPi, phosphoric acid) in a predicatable 1:1 molar ratio (p.608, right col., lns.18-28; Fig.1). The reference further teaches that PPi can be hydrolyzed to inorganic phosphate (Pi) (p.608, right col., ln.s.31-32), that detection and measurement of Pi is a measure of PCR performance (p.608, right col., lns.33-36), and describe an assay for Pi measurement (p.608, right col., lns.41-52). Durward also provides examples in which amplified DNA is detected by Pi measurement (Fig.2; Fig.3; Table 1). Because the Pi results directly from the hyrdolysis of PPi, this measuring technique is using the PPi.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have combined the allele specific amplification methods of Newton et al with the phosphate measurement detection methods of Durward et al. One would have been motivated to do so on the assertion of Druward et al that PCR measurement by phosphate detection can offer advantages in terms of speed and low cost (p.610, left col., lns.35-36). One would have had a reasonable expectation of success because Druward et al provides examples of sensitive and specific detection of PCR performance using the method (Fig.2; Fig.3).

Therefore, in view of the prior art, the claimed invention is prima facie obvious.

6. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al (1997) US Patent 5,595,890 in view of Durward et al (1998) as applied to claims 8 and 9 above, and further in view of Fujisaki at al (1999) US Patent 5,935,520.

The teachings of Newton et al in view of Durward et al are applied to claim 10 as they are applied to the rejection of claims 8 and 9 previously in this office action.

Durward et al teaches detection of PCR performance by measuring the optical density of phosphomolybdenum complex reduced by Fiske-Subbarow reagent.

Newton et al in view of Durward et al does not teach the use of a dry analytical element for the analysis of production of the PCR product.

Fujisaki et al teaches a dry analytical element for analyzing an analyte in a sample solution using a colorimetric reaction (col1. lns.39-50). The reference teaches the use of a reagent layer in the element that contains components necessary for producing a colorimetric reaction.

It would It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the methods of Newton et al in view of Durward et al to have included the dry analytical element taught by Fujisaki et al for the measurement of PCR performance. One would have been motivated to do so based upon the assertion of Fujisaki et al that such dry analytical elements provide for the simple and rapid analysis of sample solutions (col.1 lns.32-37). One would have had a reasonable expectation of success because Fujisaki et al teaches that dry analytical elements can utilize color reaction based assays (col. 1 lns.45-50) in which components necessary for the coloring reaction are contained in a reagent layer (col 8 lns.45-47), and Durward et al demonstrate that the reagents used to create the color change (molybdate and Fiske-Subbadow solution) to measure PCR performance are added sequentially to the PCR mix for the assay (p.609, middle col., lns.10-18).

Therefore, in view of the prior art, the claimed invention is prima facie obvious.

Conclusion

No claim is allowable. No claim is free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached at 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER
1/30/06